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AUTHOR Avery, Gordon B.
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ABSTRACT

Premature birth (defined as delivery before 37 weeks gestation) and low birthweight (below 2,500 grams) are major health problems in the United States. Infants in these categories account for 75 per cent of neonatal deaths and 50 per cent of deaths in the first year of life. Survivors contribute disproportionately to the pool of handicapped children who require rehabilitative care and may never be competitive individuals. Research advances and the availability of perinatal intensive care have resulted in vastly improved survival in the past decade. The weight at which roughly half the babies survive has dropped from 1300 to about 800 grams. Better care also has been associated with a better quality of life for the survivors. The vast majority of prematures greater than 1000 grams birthweight can be expected to survive, and mean IQ values of premature infants at this weight approach those of the general population. The group below 1000 grams birthweight does not participate fully in this improved prognosis. Below 750 grams, less than half survive, and a considerable number of the survivors have serious health problems. (In conclusion, 10 research areas are identified in which progress is desired.) (Author/RH)

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MATRIX NO. 1

PREMATURITY: A MAJOR HEALTH PROBLEM

by

Gordon B. Avery, M.D., Ph.D.
Director, Division of Neonatology

Children's Hospital National Medical Center
George Washington University School of Medicine

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PREMATURITY: A MAJOR HEALTH PROBLEM

Scope of the Problem

Premature birth is defined as "delivery before 37 weeks gestation," so that immaturity of the infant presents serious health problems. At times weight is used to define the at-risk population, because weight is reported more universally and is assessed more accurately. Those under 2500 grams birthweight have sharply increased morbidity and mortality. These low birthweight infants are about two-thirds true prematures (born early), and one-third small for gestational age (SGA), because of undergrowth during a pregnancy of normal length. A special high risk group is comprised of those born early who also are undergrown.

The number of infants affected with these problems is considerable. In the United States, in a year, approximately 3.6 million babies are born, of whom 7%, or 250,000, are low birthweight and 40,000 are very low birthweight (below 1500 grams). Though a minority of deliveries, these babies contribute about 75% of the neonatal deaths, and 50% of the deaths in the first year of life. The survivors may require weeks or months of highly specialized hospital care, and after discharge, contribute disproportionately to the number of handicapped children who require special rehabilitative care. Because newborns have their entire lifetime ahead of them, the quality of life of the survivors of premature birth has enormous impact.

Typical problems of the true premature flow from the immaturity of vital organs. Respiratory distress is very common and often requires prolonged ventilatory support. Nutrition is a major problem for the very small premature, and total nutrition by vein may be needed until stomach capacity enlarges and permits the gradual increase of enteric feedings, initially by tube. The premature is very vulnerable to infection, and multiple courses of antibiotics may be needed during the early weeks of life. Fluid and electrolyte management is precarious because of immature kidney function, and the premature is overloaded easily with salt and water. Special diseases unique to this era of life take their toll: necrotizing enterocolitis, retrolental fibroplasia, and intraventricular hemorrhage are particularly devastating. Apneic spells (repeated sudden cessation of breathing) require constant monitoring and frequent resuscitation. Perinatal asphyxia and low Apgar scores are more common in the smaller prematures.

The small for gestational age (SGA) infant has problems related to a suboptimal intrauterine environment, and tolerates the asphyxia of labor and delivery poorly. There is an increased incidence of stillbirth, severe perinatal asphyxia, hypoglycemia, polycythemia, meconium aspiration, and pulmonary hemorrhage. Some of the affected babies have inherent disease apart from their uterine environment, and there is an increased incidence of congenital malformations.

Outcome

The survival of the low birthweight infant has improved steadily over the last 10 years.[1] The weight at which roughly half of the infants survive has dropped from 1300 to 800 grams in well-run perinatal centers. Perhaps of greater impact on

society is the quality of the survivors. Cerebral palsy, especially spastic diplegia, affected about 60% of survivors under 1500 grams birthweight in the 1950s. This figure has dropped to less than 10%. Prematures contributed two-thirds of the children to clinics for the cerebral palsied, but this figure has dropped to one-third in a more recent estimate.[2] The vast majority of infants between 1000 and 2500 grams will now survive and be intact or have minor handicaps, given access to modern perinatal care. Some special problems, such as visual and hearing defects (1% to 2%), delayed speech, and learning difficulties in early school years, still are significant in the larger prematures.[3] The small-for-dates survivor may have particular problems with delayed speech, behavior, and school failure. In one series, the doubly disadvantaged SGA-premature had a 50% incidence of serious handicaps.[4]

The cutting edge of morbidity and mortality is presented by the infant below 1000 grams birthweight. These infants have a high incidence of intraventricular hemorrhage (50%), retrolental fibroplasia (10%), and chronic lung disease, even with expert care. Yet, fully intact survivors are seen occasionally among babies as small as 600 grams birthweight. At these lowest weights, gestational age, rather than birthweight, may be the most crucial determinant of viability.

Epidemiology of Prematurity

The incidence of prematurity, and especially of birthweight below 1500 grams, is not uniform throughout the world, or even within the United States. Because prematurity is associated with such a high morbidity and mortality, there is great interest in determining potentially preventable contributing factors. A study by Eisner *et al.*,[5] utilizing birthweight below 2500 grams as the endpoint, performed multivariate analysis on over 500,000 records and identified factors associated with low birthweight. These factors were: nonwhite race, previous reproductive loss, short interpregnancy interval, out-of-wedlock birth, absence of prenatal care, and maternal age below 18 or above 35 years. In general, these factors cluster in disadvantaged populations. The District of Columbia has an infant mortality higher than any state, but also has a low birthweight rate twice the national average, and an incidence of birthweight below 1500 grams three times the national average.

Indeed, Lee *et al.*[6] recently have shown that the incidence of very low birthweight (below 1500 grams) is the best predictor of neonatal mortality, both within the country and between nations. Although the United States ranked seventh lowest in the world in neonatal mortality (among those they studied), it was second lowest when the neonatal mortality was adjusted for the increased incidence of very small prematures. The District of Columbia, within the United States, was very similar to the mean of the 50 states, when neonatal mortality was corrected for incidence of very low birthweight. The implication is that measures designed to reduce extreme prematurity would have profound leverage upon neonatal mortality and morbidity. On the other hand, social, economic, and political contributing factors are difficult to approach from a purely medical vantage point.

Research Advances

A near revolution in neonatal care of the premature has occurred in the past decade. Elaborate electronic monitoring equipment, respirator technology, and laboratory studies performed on minute amounts of blood have permitted a more active approach.

Rh erythroblastosis, once a severe and fairly common problem, virtually has been eliminated by passive antibody treatment of the mother (Rhogam). The use of continuous distending pressure (CPAP, PEEP) has improved oxygenation in hyaline membrane disease, resulting in improved survival. Understanding of techniques of artificial ventilation, as they apply to very small babies, has allowed the majority of ventilated newborns to be successfully discharged from the nursery. The prevention of cold stress has been aided by the widespread use of servo-controlled radiant warmers in the delivery room, during procedures, and when repeated access to the baby is needed. Understanding the large contribution of radiant heat loss has resulted in double-walled incubators and other thermal barriers inside of incubators.

Biochemical and nutritional homeostasis has been much improved with the development of microchemical laboratory techniques. Calcium and glucose control, sodium balance, and acid-base balance have all profited from studies delineating the relevant physiology. The application of total parenteral nutrition to the premature has permitted continued growth at near-intrauterine rates in tiny prematures, even those with severe lung disease on the respirator. This is in contrast to the previous situation, when partial starvation during a period of rapid brain growth was commonplace. This important advance has required the use of pumps for constant, low rate infusion. Intravenous fat preparations have eliminated essential fatty acid deficiency and permitted greater caloric density and lower osmolarity. Realization of the importance of supplying adequate phosphorus, zinc, and copper has improved results. The need to supplement vitamin E in the small premature has been further defined.

Physiologic monitoring has developed rapidly and improved materially the outcome of the small premature. Transcutaneous oxygen electrodes have permitted continuous surveillance of blood oxygen tension, with potential to protect the vulnerable retina from hyperoxia and aid weaning from the respirator. Indwelling arterial and central venous catheters and pressure transducers have allowed more precise support of the circulation.

Ultrasound devices have played a particularly prominent part in the advancing technology. Doppler techniques have allowed the accurate and noninvasive measurement of systemic blood pressure. Ultrasound imaging has improved diagnosis of abdominal and intrathoracic masses. Cardiology of the newborn has been aided immensely by echo techniques. M-mode echocardiograms have permitted measurement of cardiac dimensions and electromechanical time intervals. Two-dimensional echocardiograms have partially supplanted cardiac catheterization for congenital defects, and bubble-contrast injections have allowed the delineation of shunts. Ultrasonography of the head is now becoming the preferred way of identifying intraventricular hemorrhage, delineating its extent, and following ventricular size in potential hydrocephalics.

Computerized x-ray tomography also has opened doorways of understanding. It was the advent of the CT scan that made neonatologists aware of the high incidence of intraventricular hemorrhage in the small premature, much of it clinically silent. The technique allows precise diagnosis of cysts, tumors, subdural hematomas, congenital malformations, and even subtle density changes associated with transient cerebral edema after asphyxia.

Radioisotope scans have become safe and convenient means for delineating anatomy and function of potentially malformed or obstructed kidneys and livers. They help identify localized infection. Further refinements may prove useful in defining regional blood flow and ventilation/perfusion relationships in the lung.

Happily, improved survival rates among prematures have been accompanied by decreased disability in the survivors. This overall trend has held up for the past 15 years and has been reported from many institutions. The fractional contributions are impossible to assess of improved monitoring and resuscitation, nutritional and metabolic support, maintenance of thermal neutrality, ventilatory support, and improved diagnostic accuracy.

Prematures below 1000 grams may not participate fully in this optimistic outlook. Significant mortality, accompanied by disabilities such as retrolental fibroplasia, cerebral palsy and mental retardation, the aftermath of intraventricular hemorrhage, apnea and asphyxia, and chronic lung disease suggest the research needed in the next decade. A point of diminishing returns may be defined in the premature below 700 grams, and an absolute floor to postnatal survival with currently foreseeable technology may exist at about 24 weeks gestational age.

Research Agenda for the 1980s

Ten significant research areas will be described below. These are: definition of factors causing premature delivery; monitoring and intensive care of the brain; mechanism and control of pulmonary hypertension; early diagnosis of sepsis; measurement of reserve bilirubin-binding capacity of albumin; etiology and management of necrotizing enterocolitis; nutritional support of the premature, including the mechanism of the associated cholestatic jaundice; neonatal pharmacology; the study of high frequency ventilation; the detection and prevention of Group B streptococcal disease. These areas of emphasis, in some cases, represent follow-up opportunities based on currently available information. In other instances, a problem is defined, which, until now, has resisted solution and is crucial to improved care of the premature.

Reduction of the incidence of prematurity obviously would pay enormous dividends. The variation between populations suggests that prematurity is not inevitable, but the associated factors are so global as to be relatively unapproachable. Epidemiological studies might define more tightly the specific interventions that, most efficiently, would reduce prematurity.

The long-term sequelae of prematurity are mainly the result of injury to the brain from hypoxia-ischemia or intraventricular hemorrhage. Improved techniques urgently are needed for monitoring cerebral blood flow; intracranial pressure; shifts of fluid and electrolytes within the brain; the tissue microenvironment in the brain, such as pH, pO_2, pCO_2; and lactic acid concentration. More accurate information about the state of the brain as a tissue would allow more rational management of buffering, circulatory and ventilatory support, use of vasoactive pharmacologic agents, and application of positive airway pressure. Some of these answers might be obtained by analysis of jugular venous blood or cerebrospinal fluid. Isotope scans, ultrasound, and other biophysical methods also may prove useful. In any event, the

focus of interest and advance will probably shift in the next decade from the lung to the brain of the premature.

Pulmonary hypertension, with associated persistent right to left *fetal* shunts or right heart failure, is a significant problem in newborns. It complicates meconium aspiration and asphyxia, and in prematures, often is a feature of chronic lung disease following hyaline membrane disease. Current techniques for managing this problem – fluid restriction, diuretics, hyperventilation, vasodilators – have undesirable side effects and are incompletely effective. More elucidation of the mechanisms by which pulmonary vascular resistance is controlled and the development of lung-specific vasodilating agents, perhaps members of the prostaglandins family, would be extremely valuable.

Sepsis is common and difficult to diagnose in prematures. Fever, leukocytosis, and other markers of infection often are absent. Many techniques for laboratory confirmation (NBT test, absolute band count, C-reactive protein) have proved nonconclusive, and repeated courses of antibiotics testify to our imprecision in diagnosis. It would indeed be a great boon to care of the premature if a rapid and simple laboratory aid could be devised by which the suspicion of sepsis could be confirmed or rejected.

Another long-sought, but not yet practical, laboratory test is a simple and reliable measurement of the reserve bilirubin-binding capacity of serum albumin. Rational management of jaundice requires this value, which is merely inferred from indirect bilirubin and total protein or albumin levels, with a fudge-factor for acidosis, hypoxia, prematurity, etc. A number of candidate binding capacity assays have proved unreliable or too difficult in the clinical setting. The importance of this need is illustrated by the fact that significant jaundice occurs in more than half of prematures, and that kernicterus at lower bilirubin values has been reported in these babies.

Necrotizing enterocolitis is a severe and sometimes lethal disease that affects 2% of admissions to neonatal intensive care units. It occurs primarily in small prematures, and complicates the initiation of oral feeding. Bowel ischemia, resulting from perinatal asphyxia, is certainly a factor, but occurrence in clusters strongly suggests an infectious and sometimes epidemic agent. Whether this is one or several bacteria, a virulence factor (episome or mutation) in a common bacterium, or a virus, is at this time unknown. It is, however, an important area for investigation.

Nutritional support of the premature, utilizing intravenous alimentation and intravenous fat preparations, is an important advance of the past decade. However, significant unsolved problems remain. The effect of infused amino acid mixtures on the blood amino acid pattern, and the importance of these changes, remain to be adequately assessed. Intravenous fat preparations may interfere with pulmonary function and alter serum lipid patterns. Very small prematures may be intolerant to high rates of glucose infusion. A major problem is the development of cholestatic jaundice in infants receiving intravenous alimentation for more than 6 to 8 weeks. Most cases resolve when intravenous alimentation is stopped, but a minority go on to liver cirrhosis. The mechanism of this association remains to be delineated, and a strategy to prevent liver injury needs to be devised.

The pharmacology of the newborn, especially the premature, is a critical and largely unexplored area. Kidney function is reduced markedly at birth and increases sharply during the first 6 weeks of life. There are additional variations depending on gestational age and dietary exposure after birth. The liver enzymes for drug metabolism include some that are relatively mature at premature birth, some that mature steadily with postconceptional age inside or outside the uterus, and some that are quite immature at birth and then increase rapidly. This being the case, the extrapolation of dosage schedules, from older children to newborns, or from newborns to prematures, is hazardous. The grey disease, from accumulation of chloramphenicol in prematures, is a case in point. There is, in addition, greater interindividual variation in drug half-life in the first 2 weeks of life. Ideally, pharmacokinetics should be done by gestational and postnatal age for every drug used in the newborn, and drug levels monitored when individual variation is great. At present, drug levels are available and indicated for aminophylline and caffeine, gentamicin, kanamycin and chloramphenicol, phenobarbital and phenytoin, and digitalis. It is clearly in the interest of effective care of the premature to expand this body of knowledge to include the most frequently used and toxic drugs. Over- and underdosage may be more widespread and responsible for more untoward results than we at present suspect.

Although present techniques of artificial ventilation of the premature are vastly improved, there are still babies whose lungs are destroyed by barotrauma in an effort to assist them. Animal work and adult experience with short-term ventilation during bronchoscopy suggest that very rapid ventilation (oscillation) at rates up to 1200/min (20 Hz) may result in lower peak airway pressures and better distribution of ventilation. At these frequencies, poor compliance is not of such importance, and different mechanisms of gas exchange appear to be operative. Fundamental animal research must continue to define the mechanisms of this novel style of ventilation and the optimal indications and ventilator parameters. Special equipment is needed, and application to prematures must be experimental and cautious. However, there may be indications in the premature for which high speed ventilation offers unique advantages.

Group B streptococcal disease has become common in newborns during the past decade. A particularly fulminating form presents in the first hours of life with respiratory distress, shock, and a rapid downhill course. Over 50% of the early-onset Group B streptococcal infections result in death despite the availability of appropriate antibiotics. Colonization of the mother's genital tract is so common that culture and antibiotic prophylaxis thus far have not been practical. Preliminary reports suggest that immediate penicillin treatment of the neonates, regardless of symptoms, may reduce incidence and mortality of the disease. Increase of antibiotic-resistant organisms has been noted, however, and the risk-benefit ratio of this approach must be defined further. In the meantime, this particularly common and fulminating infection must be the subject of concern and investigation.

This list of research areas by no means exhausts the unanswered questions relating to care of the premature infant. If even a portion of the answers can be found and translated into effective therapy, however, the dividend to society will be enormous.

Summary

Premature birth (less than 37 weeks gestation) and low birthweight (below 2500 grams) are major health problems in the United States. Infants in these categories account for 75% of neonatal deaths and 50% of deaths in the first year of life. Survivors contribute disproportionately to the pool of handicapped children who require rehabilitative care and may never be competitive individuals. The impact of this disability over time is enormous, as newborns have their entire lifetime ahead of them. Though making up only 7% of live births, infants below 2500 grams birthweight number 250,000 per year in the United States. Hospital bills for individual babies who are small and require prolonged intensive care range up to $100,000, and lifetime care of damaged survivors may exceed $500,000.

Research advances and the availability of perinatal intensive care have resulted in vastly improved survival in the past decade. The weight at which roughly half the babies survive has dropped from 1300 to about 800 grams. Happily, the better care that has achieved this result also has been associated with better quality of life in the survivors. The rate of the most common type of cerebral palsy, spastic diplegia, has dropped from 60% to less than 10% in surviving prematures less than 1500 grams birthweight. Better techniques of monitoring and resuscitation, nutritional support, ventilation, temperature control, and metabolic regulation have all contributed to this result. The vast majority of prematures greater than 1000 grams birthweight can be expected to survive, and mean IQ values approach those of the general population.

Unfortunately, the group below 1000 grams does not participate fully in this improved prognosis. Below 750 grams, less than half survive, and a considerable number of the survivors are damaged. Severe problems are common in these babies, of which the most serious include intraventricular hemorrhage (50%), retrolental fibroplasia (10%), sepsis (20%), necrotizing enterocolitis (10%), apneic spells (50%) and chronic lung disease (15%). Even relatively uncomplicated survivors require a hospitalization of perhaps 3 months of fastidious care to achieve discharge weight.

Ten research areas are identified in which progress would be immensely rewarding. These are: definition of factors causing premature delivery; monitoring and intensive care of the brain; mechanism and control of pulmonary hypertension; early diagnosis of neonatal sepsis; measurement of reserve bilirubin-binding capacity of albumin; etiology and management of necrotizing enterocolitis; nutritional support of the premature, including definition of the mechanism of the associated cholestatic jaundice; neonatal pharmacology; the study of high frequency ventilation; and the detection and prevention of early onset Group B streptococcal disease. It is perhaps not too sanguine to hope that funds expended in these investigations could be recouped in the lessened need to care for handicapped survivors in the future.

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